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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/465,596	06/05/95	SELDEN R	MGH87-01F4A

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EXAMINER	
LOW, C	
ART UNIT	PAPER NUMBER
1633	16

DATE MAILED: 06/08/98

Please find ~~below~~ attached a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary

Application No.	Applicant(s)
08/465,596	Selden
Examiner	**Group Art Unit**
Christopher S. F. Low	1633

☒ Responsive to communication(s) filed on *11 Mar 1998*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *72-101* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *72-101* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 11 March 1998 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

The prior pending claims 37-71 have been canceled in favor of new claims 72-101 to which the following are or remain applicable.

Objection and Rejection for New Matter

The amendment filed 11 March 1998 is objected to under 35 U.S.C. 132 because it introduces new matter into the specification. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows.

The added material which is not supported by the original disclosure is as follows: the item (a) recitation in claim 72 of " and without a viral vector, wherein the DNA sequence comprises no DNA of retroviral origin" as recited in claim 72; and, the item (a) recitation in claim 87 of "and without a retroviral vector, wherein the DNA sequence comprises no DNA of retroviral origin". The above recitation in the claims has no apparent explicit or implied antecedent basis nor any apparent definition in the in the specification as originally filed.

Where the present amendment (pages 10 and 13) refers to page 4 (lines 16-21), 5 (line 32)to page 6 (line 4), and page 6 (lines 21-25, 28-31 and 25-31) as support for the claim 72 recitation of " and without a viral vector, wherein the DNA sequence comprises no DNA of retroviral origin" as recited in claim 72 none of these pages contain any recitation that describes the claim language nor suggests the present claim language. As to the discussion (response page 13) of the item (a) recitation in claim 87 of "and without a retroviral vector, wherein the DNA sequence comprises no DNA of retroviral

origin", page 13 of the application, like pages 4-6 of the application these pages do not contain any recitation that describes the claim language nor suggests the present claim language. Thus, it is not apparent where in the written description as originally filed that the above indicated terminology is found. These pages of the application do not contain the phraseology discussed above nor do these pages of the application indicate that the genetic material used contains no retroviral DNA nor are the cited passages of the application interpretable as meaning "and without a viral vector, wherein the DNA sequence comprises no DNA of retroviral origin" nor "and without a retroviral vector, wherein the DNA sequence comprises no DNA of retroviral origin".

Rejections under 35 U.S.C. 112 first paragraph

New Matter

Claims 72-101 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention as to the presently recited new matter as discussed in the above objection to the claims.

The foregoing objects to the amendment and rejects the claims on the basis of new matter. Applicant is required to cancel the new matter in the response to this Office Action.

Enablement

Claims 72-101 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention; and claim 72 101 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which is most nearly connected, to make and/or use the invention, i.e., the claims are not enabled by the present application written description as presently claimed.

The instant application contains only one disclosed vector, example 1. That vector is pXGH5. The vector as indicated in the Selden *et al.* (1986) Molec. Cell. Biol. 6(9): 3173-3179 as containing genetic material from pUC12 which is referenced in the publication by reference 20 which is a reference by Vieira *et al.* (1981) Gene 19: 259-268. The Vieira *et al.* reference disclosed that pUC12 contains genetic material from M13, a virus. Thus, the application does not disclose a vector that contains no viral and/or no retroviral genetic material. The neither the present application nor the present response refer to any vectors that contain no viral genetic material nor any vectors that contain no retroviral material. Specification pages 4-6 and 13 that the response filed 11 March 1998 refers to have been considered in this regard and for the reasons indicated in the above objection for new matter and rejection for new matter under 35 U.S.C. 112 first paragraph, the specification does not teach or suggest the absence of viral and/or retroviral material from the vectors. There is also no explicit teaching of a vector that contains no viral DNA or no viral RNA even where the instant application disclosure indicates that there are obstacles. Pages 17+ and 33+ of the application contains no disclosure that the vectors contain no viral and/or nor retroviral DNA (retroviruses do not contain DNA). Page 35+ refers to using viral DNA as a selected gene sequence which is directly contrary to the instant claim recitation. The present claims also indicate selecting for free from deleterious integration events but does not define nor disclose how such events are to have detected and cells containing same removed from the selected cell population. In this regard, page 4 of the application contains no written description of the instant claims and no enabling disclosure that guides one skilled in the art and pages 15+ of the application do not define same.

It is noted that pages 14-21 and 22-40 discuss the prior Office Action rejection under 35 U.S.C. 112 first paragraph, however, the comments are unpersuasive in view of the above stated ground of rejection even where page 14+ cites and refers to the *Vas-Cath Inc. v. Mahurkar* decision as to one skilled in the art and to what is claimed. For the reasons indicated in the preceding paragraph, the facts in this application differ from the cited decision. As to the page 16 discussion of the Robertson *et al.* reference, the comments are also unpersuasive nor address the stated rejection. As to the discussion of proviruses (pages 16-17+, response filed 11 March 1998) the comments are unpersuasive as to teaching the recited claim terminology. As to the citation of the *Ralston-Purina Co. v. Far-Mar Co., Inc.* and the *Ex parte Yamaguchi* decisions the comments are also unpersuasive since

the even where applicant would argue that the claim need not be described literally, there is no indication that the disclosure meant to exclude virus and/or retrovirus since as discussed in the application written description, all that is indicated is that there are problems with viral and/or retroviral vectors but not that the application intended to exclude same. The lone exemplified vector contains viral genetic material. Thus, it is not apparent that the claims are supported by a written description nor does the written description enable the present claims.

The page 19+ discussion of Transkaryotic Therapies, Inc. is noted, however, the presence or the absence of the company is not an issue for enablement nor for written description of the instant claims and is unpersuasive. In this paragraph, the citation of the Selden (1987) N. Eng. J. Med. and Science references have been considered, however, the Science paper and the N. Eng. J. Med. were both published after applicant's filing date of 1 May 1987 in the 07/044,719 application nor do either reference refer to the instant '719 application and both references disclose the presence of viral genetic material in the constructs used. Thus, neither reference supports the present claims nor the application disclosure as to the resent language in the claims.

As to pages 22-40 in the 11 March 1998 response, the comments are also unpersuasive as to the page 23+ discussion regarding all genes as transferred via a nonviral and/or nonretroviral construct since those constructs are not disclosed nor *per se* suggested even where the claims (page 24) are asserted to refer to gene transfer as opposed to gene therapy. The present application does not disclose where nor indicate that the transfer is for anything but for gene therapy and that the vector used (and which is the only disclosed vector) contains viral genetic material. Thus, the claims are not enabled nor described in the application as originally filed. The page 25 discussion of gene transfer is noted, but unpersuasive as to explicit description in the application as filed nor suggestion in the application as filed nor by exemplification in the application as filed. As indicated above, the lone vector disclosed in the application contains viral genetic material and therefore, does not demonstrate the claims which are asserted to require the absence of a viral vector, i.e., a vector that contains no viral or retroviral genetic material. In this regard, the response (pages 26-27) refer to *In re Marzocchi*, *In re Jolles*, and *Application of Hartop*, *In re Brana*, *Raytheon Co. v. Roper Corp.* as to compliance with 35 U.S.C. 112 and support for broader claims. The comments are unpersuasive since the present

claims have nor explicit, implicit nor suggested disclosure in the present application as filed. As to the cited decisions, the present response does not demonstrate where in the application as filed that such disclosure is present in the application and confuses the utility guidelines under 35 U.S.C. 101 with the requirements under 35 U.S.C. 112 first paragraph as to written description and enablement based upon that written description.

Insofar as pages 28+ cite and discuss example 10 and references by Like *et al.*, Stearns *et al.*, and Schwab *et al.*, it is not clear nor apparent where in the application nor in example 10 that the references are relied upon. The references do not appear to have been cited in the application in the example nor does the response point to any part of the application that cites these references. What is not disclose (or cited in the application) cannot be used for enablement nor for written description nor for best mode. At pages 28+, the present response refers to the Geisen declaration. The declaration does not discuss the present claims and is ineffective.

The page 30+ discussion of immunosuppressive therapy is noted as asserted to be an optional embodiment, however, pages 20, 33-34, 38, 46-47, and specification examples 6-7 do not discuss, suggest, nor exemplify the presently claimed invention defined in claims 71 and 87. As to the page 31 discussion of the Cao *et al.* reference, it is published long after applicant's filing date, does not disclose the state of the art at the time the original application was filed, and does not disclose the presently claimed invention, but does disclose having used a BMGNeo vector which contained 69% bovine papilloma virus genome and thus, is a reference disclosing having used vectors containing viral genetic material and unpersuasive.

Pages 32+ assert that the specification is enabling for animals and genes not used in the examples. The comment is noted but unpersuasive as to the present claims, e.g., 72 and 87 and the claims dependent thereto and cites *Ex parte Balzarini*, however, the present claims are not supported in the application as filed by disclosure nor tests demonstrative of genetic constructs that contain no viral and/or nor any retroviral genetic material. In the present application, there are no disclosed tests of the instant vectors that are recited in the claims as having no viral and/or no retroviral genetic material. Thus, the facts differ from that of *Ex parte Balzarini*, however, the rejection present rejection

is not for scope but for nonenablement which is issue under 35 U.S.C. 112 first paragraph considered in the "REJECTION 1" indicated in the decision and is affirmed.

The discussion (pages 33+) of the Orkin *et al.* and the Crystal references is noted, but unpersuasive as to the present claims for the reasons indicated above. At page 36, applicant's response refers to the *In re Glass* and the *U. S. Steel v. Philips Petroleum Co.* decisions as to references discussing the state of the art after applicant's filing is noted, however, neither the response nor the decisions indicate how the state of the art is more advanced or enabling at the time of filing than some several years later. When the art cited considers and presents doubts as to success at a time after applicant's filing, it cannot be said that at a time prior, that the application was enabling.

At pages 37+ applicant's response refers to others as recognizing novel/pioneering work by citing the Kawakami *et al.* (1992) Diabetes 41: 956-961, however, the reference disclosed having used a vector that contained 69% papilloma virus sequences. Thus, the reference does not demonstrate applicant's claim and indicates that 1/10th of the material was used compared to references 2 and 4 cited in the Kawakami *et al.* reference wherein the Kawakami *et al.* reference did not even use a vector that contained no viral genetic material nor is such predicted by the present application disclosure. The discussion of the Simpson *et al.* (1995) Gene Therapy 2: 223-231 reference is also noted as to the reference to "footnote 2" but page 223 contains no footnote. As to the comment of referring to reference 2 that is cited at page 230 of the Simpson *et al.* reference, the Selden *et al.* reference in the N. Eng. J. Med. does not disclose a vector that was used that had no viral genetic material but does disclose pHINT5 which contains genetic material from pUC18 (figure 4 of the Selden *et al.* reference) which absent factual evidence to the contrary, contains genetic material from a virus and pHINT5 is not apparent nor disclosed in the present application and the reference disclosed that the mice died of transkaryotic implantation induced hypoglycemia, i.e., the reference demonstrates a lack of control of gene expression. At page 38, it is also noted that the response refers to a reference by Lauffenberger *et al.* (1996) and especially page 71 column 1 as to nonviral gene therapy. It is noted that the Lauffenberger *et al.* reference refers to the Selden *et al.* reference in the N. Eng. J. Med. which for the above discussed reasons is unpersuasive and does not show the presently claimed invention. As to

each of the Kawakami *et al.*, Simpson *et al.*, and Lauffenberger *et al.* references, each is published after the present application was filed in 1987 and thus, cannot be used to show enablement.

The comments at pages 38-40 of the response filed 11 March 1998 have been considered as to the comments regarding citation of the Rosenberg *et al.* "Reports" reference (but is really an article taken from Science but the reference does not disclose nor indicate using vectors that contain no viral and/or no retroviral genetic material and even the reference at page 1577 to Selden is a reference to Selden *et al.* (1987) Science 236: 714-718 where the Selden *et al.* (1987) Science 236 reference refers to having used pXGH5 which vector as discussed above contains viral genetic material and does not demonstrate the present claims. As to the pages 38-39 discussion of the Tani *et al.* reference and acknowledgment at page 1274, column 1 of the Tani *et al.* reference, also refers to the Selden *et al.* (1987) Science and for the reasons indicated above and in the preceding paragraphs, the comments are unpersuasive as to the present claims. Similarly, the Malik *et al.* and Ogura *et al.* references refer to the Selden *et al.* (1987) Science reference, whereas Teumer *et al.* refers to the Selden *et al.* (1986) Molec. Cell. Biol. publication and Yanagita *et al.* refer to the Selden *et al.* N. Eng. J. Med. references and each does not demonstrate a vector that contains no viral and/or nor retroviral genetic material. It is also noted that page 40 refers to references by Rosenthal *et al.* and Moritani *et al.* however, for the above reasons, where these references refer to a publication by Selden *et al.*, the references do not disclose nor indicate nor demonstrate a vector that contains no viral and/or nor retroviral genetic material In view of the foregoing, the comments in the response are unpersuasive.

Obviousness-type double patenting rejections

The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome actual or provisional rejection(s) based on non-statutory double patenting ground(s) of rejection set forth below provided the conflicting application(s) or patent(s) is/are shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 72-101 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over pending claims 91-126 in copending application Serial No. 08/461,292. Each of the applications contain claims in which a processes of implanting transformed cells is recited where the transformed cells express DNA that was inserted into the cells prior to implantation.

Claims 72-101 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 44 in copending application Serial No. 08/460,902. Each of the three applications contain claims to processes of implanting transformed cells where the transformed cells express DNA that was inserted into the cells prior to implantation. Here, altering the concentration of a gene product is the same as expressing the gene to produce a product in the '292 application and of putting those cells which express the gene into a host as in the '902 application.

Claims 72-101 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims in copending application Serial No. 08/465,582. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are an obvious variation of the claims in the pending '582 application since in each application but in different words, the sets of claims recite implanting a transformed cell to produce an effect in a human, i.e., *in vivo* therapy which implants a cell or cells but which cells have, *ex vivo*, been transformed prior to implantation. The present claims also do not define over the interference count. Regardless of the vector, viral or nonviral and which in this

instance, the vectors are obvious variations of effecting gene transfer into the implanted cells, the process of therapy and the intended end result is the same.

Claims 72-101are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 108-116 of copending application serial no. 08/451,894. Although the claims are not identical, each set of claims recite providing a genetically altered cell to a mammal (copending application) or to an animal (present application) each of which deliver a gene construct to cells which are then reintroduced into the animal. Therefore, the two applications claim the same inventive concept.

Claims 72-101 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 68-77 and 105-107 of copending application serial no. 08/446,909. Although the claims are not identical, each set of claims recite a process of providing genetically altered cells (in the copending application, the DNA encoding erythropoietin is a desired gene such as recited in the present application claims) to a mammal (copending application) or to an animal (present application) each of which isolate the cells, introduce the genetic material into cells, and then reintroduce selected genetically altered cells into the animal.

Claims 72-101 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 96-104 of copending application serial no. 08/446,912. Although the claims are not identical, each set of claims recite a process providing a genetically altered cell (in the copending application, the DNA encodes a glucagon-like peptide 1 is a desired gene such as recited in the present application claims) to a mammal (copending application) or to an animal (present application) each of which transfer a gene to the cells and then reintroduce the cells into the animal. Therefore, the two applications claim the same inventive concept.

Claims 72-101 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 125-134 of copending application serial no. 08/443,936. Although the claims are not identical, each set of claims recite a process which provides genetically altered cells (in the copending application, the DNA encodes a therapeutic peptide

is a desired gene such as recited in the present application claims) to a mammal (copending application) or to an animal (present application) each of which also indicate the transfer of genetic material. In both applications, the genetic material is for expression by the implanted or administered cells. Therefore, the two applications claim the same inventive concept.

As to each of the above stated rejections for obviousness type double patenting, the comments at page 22 of applicant's first submission under 37 C.F.R. 1.129 have been considered as to traversal by "deal with on the merits when the subject application is found to contain allowable subject matter". The comments are unpersuasive because these would be standing grounds of rejection and no claims are allowable with a standing ground of rejection.

35 U.S.C. 112 second paragraph rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 72-101 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 72 and 87, it is not clear whether it is the cells that do not have a viral vector or whether it is the DNA sequence that has no viral DNA. In clams 72 and 87 it is also not clear whether the "and without a viral vector" means no viral DNA or whether it is to mean that a virus is not the transforming genetic material. Claims 78, 84, 85, 93, and 99 are unclear as to what steps are included or excluded in "involves" recited in the claim as opposed to "has a step". In claims 79 and 94, it is not clear whether the cells are of the same species as that of the animal from which the cells were obtained or of the same species as the animal into which the cells are to be implanted. Claims 80 and 81 do not further limit claim 73 nor claim 72, and, claims 95 and 96 do not further limit claims 88 nor 87 because both claim 72 and 87 require the absence of viral genetic material which therefore means that there is no viral promoter nor any retroviral promoter that can be included in claim 72 nor claim 87. Claim 101 lacks antecedent basis in claim 88 and 87 for "in the genome of the recipient subject". In

claims 85 and 100 it is not clear what is the deleterious integration event to which the claim refers nor how a preexisting deleterious event is eliminated nor whether or not the transforming event eliminates a deleterious integration event. In claim 84 and 99, it is not clear what are the "desired regulation properties" and whether or not the regulation affects the genetic material that is added to the cell or whether the regulation affects some other preexisting genetic material in the cells prior to transfection.

Claims 80 and 81 are rejected under 35 U.S.C. 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 80 and 81 do not further limit claim 73 nor claim 72, and, claims 95 and 96 do not further limit claims 88 nor 87 because both claim 72 and 87 require the absence of viral genetic material which therefore means that there is no viral promoter nor any retroviral promoter that can be included in claim 72 nor claim 87.

Regarding the stated rejection under 35 U.S.C. 112 second paragraph, the comments in the first submission filed under 37 C.F.R. 1.129 are unpersuasive and are not directed to the above stated rejection.

35 U.S.C. 102 and 103 rejections over art

Insofar as applicant has amended all of the claims, the following are applicable to pending claims 72-101 as directed solely to compositions.

Claims 72-101 are provisionally rejected under 35 U.S.C. 102(f) or (g) or in the alternative, under 35 U.S.C. 103(a) as being unpatentable over the count and disclosure of the application of the winning party in the interference, which count recites a method of therapy in which cells are transformed and then implanted into the host human or other mammal after selection *ex vivo* which are the presently recited cells in the process claims.

Claims 72-75, 78-90 and 93-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined references of Salser *et al.* (US 4,497,796) and Anderson (1984) Science 226: 401-408.

Salser *et al.* disclosed a process (column 1-2 *et seq.*) in which cells were genetically altered to contain modified genes (a wide variety of genes, columns 2-4). The cells were reintroduced (column 2+) in a variety of ways (column 6) into the mammal and directed, via the gene construct(s), expression of the exogenous DNA (see at least column 3+). See at least the abstract and the claims. The reference also teaches (column 5) that among the vectors used, certain combinations such as cell fusion and, e.g., using a plasmid such as indicated in the Salser *et al.* and the Anderson references (Anderson at 406+) are expected to not contain viral or retroviral genetic material. In the disclosed process, the reference (column 2) teaches maintaining the cells *in vitro* (i.e., cloning and expanding the cells) so as to be returned to the host in a viable state (i.e., absence of deleterious integration events such as inviable cells) and so as to provide the added genetic function in a form which is useful to the host which is a teaching to culture the cells *in vitro* and to use the cells that contain and express the added genetic function in a form which is useful to the host, i.e., in alternative language to the present claims, a teaching of selecting cells possessing the desired characteristics. Here, where Salser *et al.* do not explicitly indicate a promoter type (column 4-5), Salser *et al.* nevertheless indicated obtaining expression and of constitutive and/or semiconstitutive production (column 4) and for expression a promoter is necessarily present. Here, where the Salser *et al.* reference does not explicitly indicate a promoter type, the Anderson reference disclosed (page 405-406) that various types of expression control DNA were known and had been used to regulate expression. Note that it would have also been obvious to anyone of ordinary skill in the art that autologous cells would have minimized adverse immunological effects of the implanted cells and the host animal.

The comments (pages 40-49) in the response have been considered insofar as they pertain to the above two references (both of record) but the comments are unpersuasive. As to the Salser *et al.* reference, applicant's response (pages 47-48) asserts methotrexate is disclosed as used in the Salser *et al.* reference, however, the reference indicates (column 6) that upon cessation of the treatment, the cells continue to proliferate and are maintained as a high level for extended periods of time and at column 1-2 indicates that such stressing of the host is optional. The discussion at page 48 regarding promoters and the Salser *et al.* reference is noted, but for the reasons indicated in the stated rejection the comment is unpersuasive. As to the Anderson reference, pages 40-49 do not appear to contain

any discussion thereof but the reference nevertheless teaches vectors that do not contain viral or retroviral genetic materials as discussed in the above stated rejection.

Claims 76, 77, 91, and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined references of Salser *et al.* (US 4,497,796) and Anderson (1984) Science 226: 401-408 as applied to claims 72-75, 78-90 and 93-101 above and further in view of Sugimoto *et al.* (US 4,621,053).

Salser *et al.* and Anderson are applied as indicated above and where the Salser *et al.* reference indicates proteins such as hormones (column 2) it would have been obvious to one of ordinary skill in the art that both insulin and hormones such as growth hormone as both genes are known and both genes are discussed in the Sugimoto reference which teaches implanting cells that have been genetically altered to produce hormones and disclosed among other genes, those for insulin and growth hormone (column 2). See also column 4+ and column 6 which disclosed that

> "As long as the "hybridoma" cell line is basically a lymphoblastoid line, preferably of leukemic origin, which contains the genes governing the production of the human peptide hormone in question, it may be used in the process of the present invention. For example, the human peptide hormone production governing genes may be introduced into the lymphoblastoid line, preferably of leukemic origin, by means of genetic engineering techniques, such as recombinant DNA techniques, using enzymes such as DNA ligase, nuclease, and DNA polymerase. Thus, the term "human X human hybridoma lymphoblastoid line capable of producing human peptide hormone" as used throughout the present specification and claims is intended to include not only lymphoblastoid lines produced by cell fusion between parent human cells inherently capable of producing the human peptide hormone and the human lymphoblastoid line, but also to human lymphoblastoid lines which have been altered in any manner, such as by genetic engineering, so as to be capable of producing human peptide hormone.

Thus, where the present claims indicate no viral and/or no retroviral DNA, the vectors used in the combined references do not contain virus nor any retrovirus and that from the combined disclosure of the Salser *et al.* Anderson and Sugimoto *et al.* references, it would have been obvious to have delivered a cell that had been screened for production of, e.g., insulin and/or growth hormone into a host animal. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

No claim is allowed.

Each of the Eppstein *et al.* patents cited on the PTO 1449 disclosed stable transfected cells where the transforming genetic material encoded insulin and/or growth hormone and where the cells were transfected *in vitro* prior to implantation to introduce the desired gene into a host animal.

It is noted that page 50 of applicant's response requests an interview in the event that the claims are not in condition for allowance. The present claims are not allowable. It is suggested that after receipt of the Office Action that applicant consider whether or not an interview is necessary.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to the undersigned examiner at Group 1600, Art Unit 1633.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Low whose telephone number is (703) 308-2923. Inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission to Group 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1) and must conform to the notice published in the Official Gazette, 1096 OG 30 (15 November 1989). The telephone number assigned to Art Unit 1633 in the CM1 PTO Fax Center is (703) 308-4312.

CSFL
5 June 1998

Christopher S. F. Low

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1600